UNIVERSITY OF THESSALY
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"Assesing the quality of observational studies in Human Papilloma Virus (HPV) vaccines in cervical cancer prevention using the STROBE statement"

Postgraduate Programme (MSc)
"Research Methodology in Biomedicine, Biostatistics and Clinical Bioinformatics"

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CONTENTS

ABSTRACT

PURPOSE: A substantial amount of clinical and public health knowledge originates from observational studies. Many analysis of epidemiological studies suggested that there is need for guidance in reporting observational studies and that recommendations on the reporting of research can improve reporting quality. The aim of this study was to evaluate the reporting quality of observational studies concerning cancer.

METHODS: PubMed datatabase was searched for assess in the reporting quality of observational studies (cohort, case-control, cross-sectional) of Human Papilloma Virus (HPV) vaccines in cervical cancer prevention. Quality of reporting was evaluated according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement, a checklist of 34 items/ sub-items items that are considered essential for good reporting of Observational Studies. We also compared the reporting quality in journals endorsing the STROBE statement versus journals not endorsing the STROBE statement.

RESULTS: The research strategy, using the PubMed database, identified 5645 potentially eligible studies. After retrieving and screening, a total of 25 articles were evaluated using STROBE statement as a guideline. Overall, five items/sub-items were reported by 90% or more of the studies. Furthermore, fourteen items/ sub-items were reported by 70% or more of the studies. In contrast, some items were reported only by a small fraction of articles. Also, 20% of articles reported < 15 items in the STROBE checklist and about 8% of articles reported > 23 items. Mostly articles reported about 19–22 items in the STROBE checklist. At last, articles published in 2016 have the highest average score (22 items), in contrast to articles published in 2011 have the lower average score (17 items). In comparing the reporting quality of the two groups of journals (endorsing or not STROBE statement) significant differences were seen only in two items: in the reporting of all statistical methods (item 12a) with p-value 0.022 and in the reporting of the source of funding (item 22) with p-value 0.011.

CONCLUSION: Reporting of observational studies about HPV vaccines in cervical cancer prevention is not clear. Our attempt to assess the reporting quality of observational studies in this topic of epidemiology emphasizes the need for improvement.

INTRODUCTION

Cancer is typically classified as a leading non-communicable disease. Cervical cancer is a cancer arising from the cervix. Worldwide, cervical cancer is the third most common cancer in women and the fourth most common cause of death in women. Cervical cancer is by far the most common HPV-related disease. Virtually, all cases of cervical cancer can be attributable to infection by high-risk HPV viruses. The most common of the high-risk strains of HPV are types 16 and 18, which cause about 70% of all cervical cancers. Cervical cancer can often be prevented through screening in order to find any precancers so they can be treated. Checking the cervix by the Papanicolaou test (Pap smear) and the use of prophylactic vaccines against HPV have been credited with dramatically reducing the number of cases and mortality of cervical cancer.

HPV vaccines are used to prevent HPV infection and therefore cervical cancer. All three of the HPV vaccines, Cervarix, Gardasil, and Gardasil 9, can prevent most cases of cervical cancer in females, if given before a person is exposed to the virus. Two HPV vaccines, Gardasil and Gardasil 9, can prevent many cases of vaginal and vulvar cancers in women, as well as most cases of anal cancer and genital warts in both females and males. In more details about their mechanism of action, Gardasil delivers HPV-6, -11, -16 and -18 L1 protein, conferring protection against these HPV strains, presumably through induction of humoral immune response. Cervarix is a non-infectious recombinant, AS04-adjuvanted vaccine that contains recombinant L1 protein, the major antigenic protein of the capsid, of oncogenic HPV types 16 and 18. The efficacy of the vaccine may be mediated by the development of IgG neutralizing antibodies directed against HPV-L1 capsid proteins generated as a result of vaccination.

All three HPV vaccines have been tested for safety and efficacy in tens of thousands of people in many countries worldwide. They have been examined thoroughly with similar profiles in the vaccinated and control groups, regardless of age or ethnicity. So far, no serious side effects have been shown to be caused by the vaccines. The most common side effects of vaccination are headaches, pain, redness and/or swelling at the site of injection. These problems are similar to those commonly experienced with other vaccines. More severe side effects such as anaphylactic (allergic) reaction are extremely rare. So far, the rate of adverse side effects related to immunization was consistent with what has been seen in the safety studies carried out before the vaccine was approved and were similar to those seen with other vaccines.

The vaccines have not been sufficiently tested during pregnancy and, therefore, should not be used by pregnant women. Studies show that HPV vaccines do not cause problems for babies born to women who were vaccinated while pregnant, but more research is still needed. A pregnant woman should not get any doses of either HPV vaccine until her pregnancy is completed.

Moreover, HPV vaccines are approved for males in several countries. Studies have approved that HPV vaccines reduce the risk of genital warts and precancerous lesions caused by HPV. This reduction in precancerous lesions might be predicted to reduce the rates of penile and anal cancer in men.

A substantial amount of clinical and public health knowledge originates from observational studies (OS) (1). Observational studies have a role in research into the benefits and harms of medical interventions (2). The choice of an OS design may stem from a variety of reasons such as ethics, restrictions in study planning, or feasibility. In addition, OS may be more suitable to detect rare or late adverse effects of interventions compared to randomized trials (3). Moreover, OS are often less expensive, and they can be performed over shorter time-intervals. Particularly, in cancer epidemiology, clinical trials are often not feasible because it is unethical to expose individuals to a potential cause of disease simply to explore the etiology of the disease (4).
Observational studies are the primary type of epidemiological study used to research determinants of outcome. Like all epidemiological studies, an observational study observes causes, preventions, and treatments for outcome. In observational studies, the researcher observes and systematically collects information, but does not try to change the people (or animals, or reagents) being observed. There are 4 main types of observational studies : Case-control study: study originally developed in epidemiology, in which two existing groups differing in outcome are identified and compared on the basis of some supposed causal attribute. Cross-sectional study: involves data collection from a population, or a representative subset, at one specific point in time. Cohort study study: a particular form of longitudinal study where a group of patients is closely monitored over a span of time. Ecological study: an observational study in which at least one variable is measured at the group level.

Many analysis of epidemiological studies suggested that there is need for guidance in reporting observational studies and that recommendations on the reporting of research can improve reporting quality. Readers need to know what was planned (and what was not), what was done, what was found, and what the results mean. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Initiative developed recommendations on what should be included in an accurate and complete report of an observational study. The STROBE Statement consists of a checklist of 22 items, confined for the three main analytical designs that are used in observational research: cohort, case-control, and cross-sectional studies. These items relate to the title, abstract, introduction, methods, results and discussion sections of articles. Eighteen items are common to cohort studies, case-control studies and cross-sectional studies and four are specific to each of the three study designs. A general checklist and separate checklists for each of the three OS designs (cohort, case-control, and cross-sectional studies) are available at the web site www.strobestatement.org

Although there is a considerable number of studies evaluating the quality of reporting in randomized studies, there are very few studies that critically evaluate the epidemiological literature according to the STROBE statement (5).
In the present study, we critically appraise the quality of reporting of 25 OS in cervical cancer prevention through HPV vaccines, according to the STROBE statement.

METHODS

DATA SOURCES, SEARCH STRATEGIES AND STUDIES SELECTION

PubMed database was searched for observational studies investigating Human Papilloma Virus (HPV) vaccines in cervical cancer prevention, published the last 10 years. We designed a PubMed formula as follows: the tag term used was “HPV vaccines” and the search was limited to observational studies for the last ten years, in English language and on human species.
Then, the individual articles considered eligible were retrieved in full text and further evaluated. These articles were eligible if they were OS (i.e., cohort, case-control, and cross-sectional), investigated HPV vaccines in cervical cancer protection, and had been published as full papers or short reports in a regular issue or supplement of peer-reviewed journals indexed in PubMed. Articles published as reviews, notes, letters, editorials were excluded. Figure 1 represents the study selection process. PubMed identified 5645 studies for the last 10 years. Their titles and abstracts were assessed according to the following exclusion criteria: (1)limited to observational studies, (2)reviews, notes, letters, editorials, (3)non-English language, (4)non-human studies.

DATA EXTRACTION AND REPORTING ASSESSMENT TOOL

The reporting quality indicates whether the necessary information for observational studies was sufficiently reported. The Strengthening the Reporting of Observational Studies in Epidemiology Statement (STROBE) checklist was used to score the reporting quality. In total, 34 items/sub-items were considered (Table 1). In order to clarify whether an item is accurately reported in the articles, we took into account the guidance provided by the STROBE Explanation and Elaboration document (6). All the 34 items were examined in terms of whether they were stated or not. Items were to be scored as ‘‘yes’’ if they were stated in enough detail so that they allowed the reader to decide that the definition existed in the article. Alternative or indeterminate responses (apart from ‘‘yes’’ or ‘‘no’’) to each question were coded as negative responses. The studies with reporting quality scores under 13 or with insufficient temporal information between exposure and outcome were considered to be of low quality, those between 14 and 18 score of medium quality, and over 18 score of high quality. In the Annex is represented the process of scoring, using “1” for positive and “0” for negative responses.

METHODOLOGICAL EVALUATION

The evaluation of the articles took place concerning the following sections: Introduction, Methods, Results, Discussion. Although, the most essential sections are the Methods and Results. At first, introduction items refer to the reporting of the background &rationale, and the objectives. Furthermore, methodological items refer to the reporting of study design, setting of the study, participants’ information (eligibility criteria, sources and methods of selection, or matching criteria if relevant), definition of all variables used, data sources and

methods of measurement, any efforts to address potential sources of bias, study size, handling of quantitative variables in the study and performed statistical methods (i.e., methods used to control for confounding and to examine subgroups and interactions, methods of handling missing data or how loss to follow-up was addressed, methods of matching of cases and controls, analytical methods taking account of sampling strategy and any description of sensitivity analysis). Also, the items in the results section of the STROBE statement refer to the reporting of participants' information (numbers of individuals at each stage of the study, reasons for nonparticipation at each stage, use of flow diagram), descriptive data (characteristics of study participants, numbers of participants with missing data, summary of follow-up time), outcome data (numbers of outcome events or summary measures), main results (unadjusted or confounder-adjusted estimates and their precision, presentation of 95% confidence intervals, category boundaries when continuous variables were categorized and translation of estimates of relative risk to absolute risk for a meaningful time period), and other analyses done (e.g., analysis of subgroups and interactions, and sensitivity analyses). Finally, the items in the discussion section refer to the reporting of key results, limitations of the study, interpretation and generalisability of the results.

STATISTICAL ANALYSES

The articles separated in two groups, those that their journals were endorsing the STROBE statement versus those that their journals were not endorsing the STROBE statement. Comparisons between the two groups were performed by calculating the p-value for the Chi-Square test for each item and then the Odds Ratio (OR) and the respective 95% confidence interval if there was any significant difference between the two groups. The cutoff point for statistical significance was set at the two-sided 0.05 level. Statistical analyses were done with IBM SPSS Statistics version 22.

RESULTS

ELIGIBLE ARTICLES

The research strategy, using the PubMed database, identified 5645 potentially eligible studies. Thereafter, these articles were retrieved and screened for eligibility: 5615 articles were excluded because of their study design, i.e. not observational studies, and 5 articles excluded because they did not fulfill the inclusion criteria, all of which led to a total of 25 articles. Twelve articles were identified as duplicates. Consequently, a total of 25 articles were evaluated using STROBE statement as a guideline. Figure 1 displays the whole retrieving and screening process. A full list of the 25 reports that were included in the final analysis is found in the section "References".

STUDY CHARACTERISTICS

The 25 eligible articles were published during the period 2010–2016, after the issuing of STROBE statement. Cohort studies were more frequent (64%) than cross-sectional studies (32%) and less frequent were the case-control studies (4%).

MAIN RESULTS

Table 1 shows the overall proportion of articles reporting each item in the STROBE checklist. Also, Figure 3 summarize all the results and on Table 3 are displayed the items in the checklist that are reported more than 75% and less than 25%. Overall, five items/sub-items were reported by 90% or more of the studies. The items include: 1) an informative and balanced summary, 2) the background and rationale of the investigation, 3) the objectives, 4) key results in discussion, 5) the limitations of the study. Furthermore, fourrteen items/ sub-items were reported by 70% or more of the studies. The eight additional items were: 1) the study's design in title/abstract, 2) the setting of the study (locations and relevant dates including periods of recruitment, exposure, follow-up, and data collection), 3) the reporting of eligibility criteria for participants (sources and methods of selection), 4) the description of all statistical methods (including those used to control for confounding), 5) the reporting of the study participants' characteristics (demographic, clinical, social), 6) the details of outcome data, 7) the reporting of estimates and their precision in the results, 8) overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. In contrast, some items were reported only by a small fraction of articles. For example, only 28% of articles provided the matching criteria if used, only 20% provided the reporting details about how quantitative variables were handled in the analyses and only 16% provided details about how missing data were addressed in the analyses, .The presentation of details about the number of participants with missing data and reporting of absolute risk for a meaningful time period were very uncommon, with a frequency of 4% and 8%, respectively.

Table 2 shows the proportion of reported items per article. Overall, 20% of articles reported < 15 items in the STROBE checklist and about 8% of articles reported > 23 items. Mostly articles reported about 19–22 items in the STROBE checklist.

Also, Figure 2 displays the average STROBE score of the studies per year. We can notice that articles published in 2016 have the highest average score (22 items). Although, articles published in 2011 have the lower average score (17 items).

In comparing the reporting quality of the two groups of journals (endorsing or not STROBE statement) significant differences were seen only in two items: in the reporting of all statistical methods (item 12a) with p-value 0.022, OR 0.078 (CI 0.006-0.967)and in the reporting of the source of funding (item 22) with p-value 0.011, OR 0.444 (CI 0.265-0.745). The journals endorsing the STROBE statement appear to have a better reporting in these

items. None of the other items resulted in statistical differences in the two groups. An item by item comparison is presented in Table 4.

DISCUSSION

The present study evaluated the reporting quality of published observational studies in HPV vaccines in cervical cancer prevention, using the STROBE checklist as a reference. In total, 25 articles selected from PubMed database published from 2010 to 2016 were evaluated, covering a publication period of 7 years. Although the overall reporting quality was relatively good (17 items/sub-items were reported by 74% or more of the studies) with some items being reported almost consistently, there are some essential methodological aspects (such as matching, absolute risks, flow diagram, and missing data) that are underreported, making it difficult for the reader to assess explicitly the validity of an observational study. Also, the journals endorsing the STROBE statement appear to have a better reporting in two items (all statistical methods and source of funding).

This is a novel study and in our view the first study which analyzed observational studies in the field of HPV vaccines in cervical cancer prevention. The results have direct relevance for authors, readers and editors of biomedical research. A limitation of our study is that the literature search was restricted to PubMed database and we did not extend our search to more databases. However, the number of retrieved articles provided a relatively large and diverse sample that provided an overview of reporting quality in this field of research.

CONCLUSION

We conclude that reporting of observational studies about HPV vaccines in cervical cancer prevention is not clear. Our attempt to assess the reporting quality of observational studies in this topic of epidemiology emphasizes the need for improvement. So, authors and editors should focus on this issue when reporting or reviewing reports of observational studies.

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Figure 1 **Flow diagram of citations through the retrieval and the screening process.**

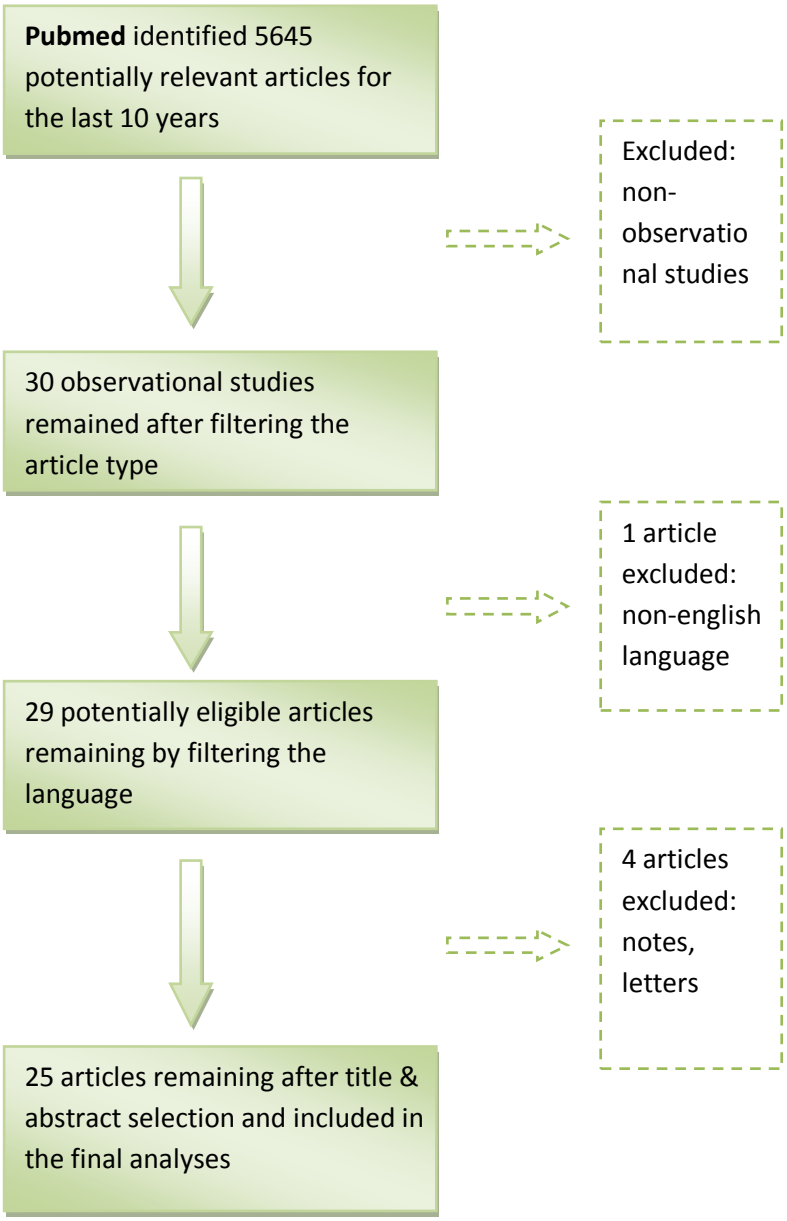

Figure 2 The average STROBE statement score of the studies per year

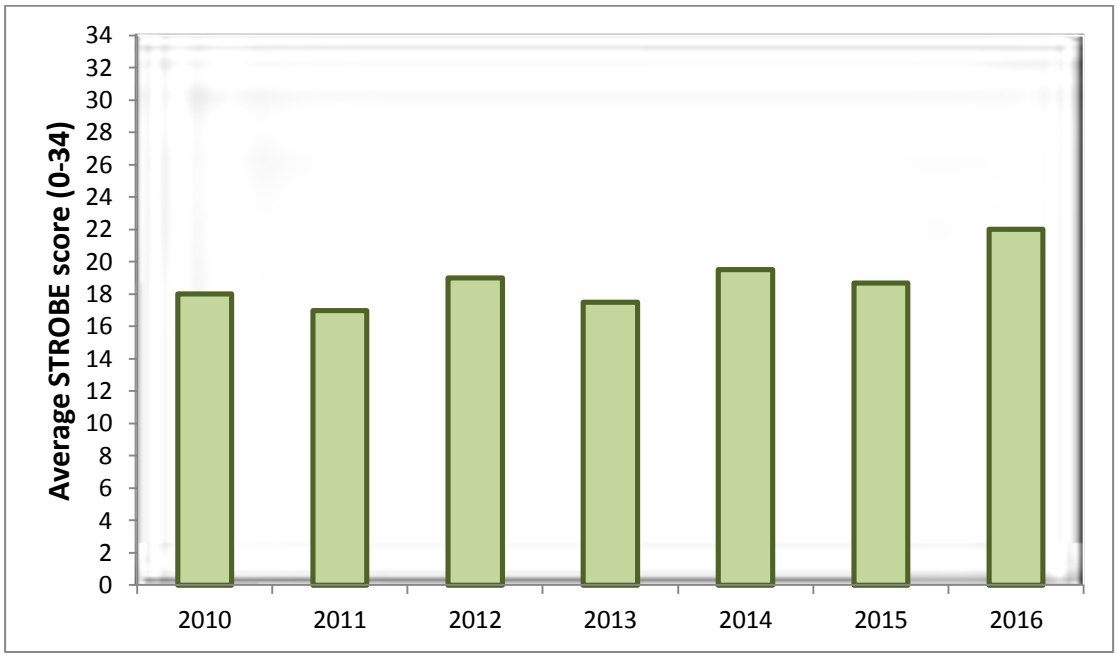

Figure 3 Summary table of all results.

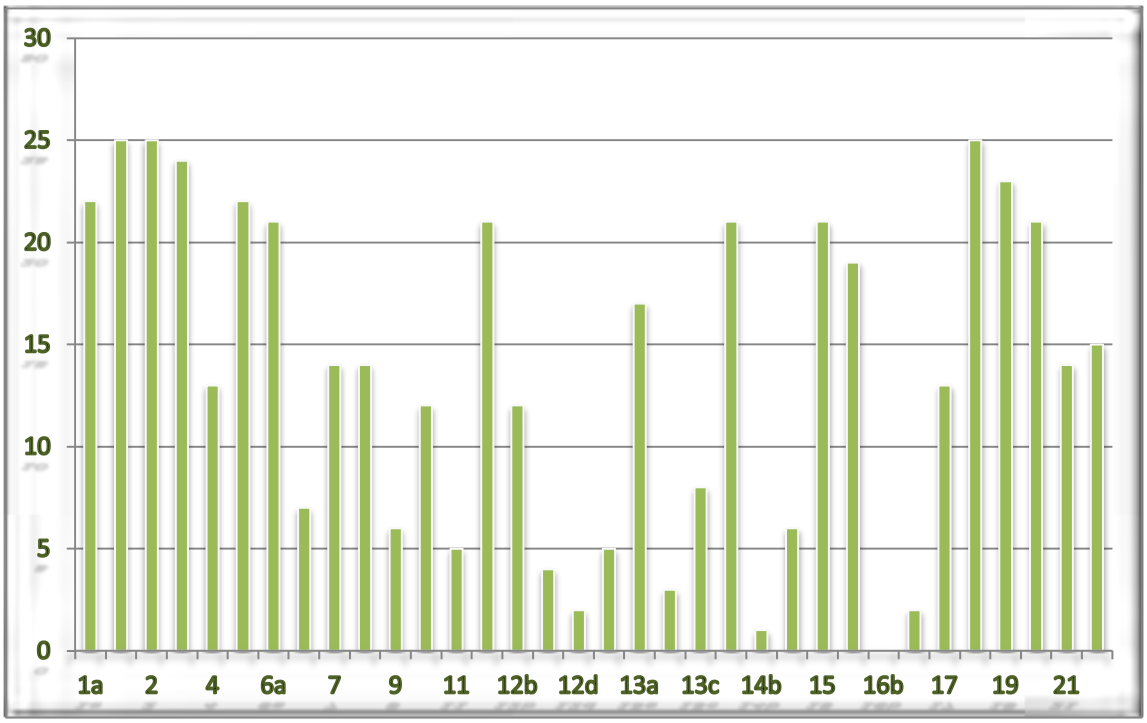

Table 1 **Number of articles that fulfill each recommendation of the STROBE Statement.**

Section	Subsection	Code	Recommendation	Articles that fulfill each STROBE recommendation (%)
Title & Abstract	Title & Abstract	1a	Indicate the study's design with a commonly used term in the title or the abstract	22 (88%)
		1b	Provide in the abstract an informative and balanced summary of what was done and what was found	25 (100%)
Introduction	Background /rationale	2	Explain the scientific background and rationale for the investigation being reported	25 (100%)
	Objectives	3	State specific objectives, including any prespecified hypotheses	24 (96%)
Methods	Study design	4	Present key elements of study design early in the paper	13 (52%)
	Setting	5	Describe the setting,locations, and relevant dates,including periods of recruitment,exposure,follow-up, and data collection	22 (88%)
	Participants	6a	*Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	21 (84%)
		6b	*Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	7 (28%)
	Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	14 (56%)
	Data sources/	8	For each variable of interest, give sources of data and details of	14 (56%)

	measurement		methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
	Bias	9	Describe any efforts to address potential sources of bias	6 (24%)
	Study size	10	Explain how the study size was arrived at	12 (48%)
	Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5 (20%)
	Statistical methods	12a	Describe all statistical methods, including those used to control for confounding	21 (84%)
		12b	Describe any methods used to examine subgroups and interactions	12 (48%)
		12c	Explain how missing data were addressed	4 (16%)
		12d	*Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	2 (8%)
		12e	Describe any sensitivity analyses	5 (20%)
Results	Particiants	13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	17 (68%)
		13b	Give reasons for non-participation at each stage	3 (12%)
		13c	Consider use of a flow diagram	8 (32%)
	Descriptive Data	14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	21 (84%)
		14b	Indicate number of participants with missing data for each variable of interest	1 (4%)
		14c	*Cohort study*—Summarise follow-up time (eg, average and total amount)	6 (24%)
	Outcome Data	15	*Cohort study*—Report numbers of outcome events or summary measures over time	21 (84%)

			Case-control study—Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study*—Report numbers of outcome events or summary measures	
	Main results	16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	19 (76%)
		16b	Report category boundaries when continuous variables were categorized	2 (8%)
		16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13 (52%)
Discussion	Key Results	18	Summarise key results with reference to study objectives	25 (100%)
	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	23 (92%)
	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	21 (84%)
	Generalisability	21	Discuss the generalisability (external validity) of the study results	14 (56%)
Other Information	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15 (60%)

Table 2 **Proportion of reported items per article**

Number of items in the checklist addressed	Number and percentage of articles reporting (n=25) (%)
0-3 items	0 (0.0%)
3-6 items	0 (0.0%)
7-10 items	0 (0.0%)
11-14 items	5 (20.0%)
15-18 items	6 (24.0%)
19-22 items	12 (48.0%)
23-25 items	2 (8.0%)
25-34 items	0 (0.0%)

Table 3 **Items in the checklist usually reported and usually not reported**

Items reported by <25% of studies	Items reported by >75% of studies
Number of participants with missing data (item 14b) 4%	Informative and balanced summary in abstract (item 1b) 100%
Estimates of relative risk into absolute risk for a meaningful time period (item 16c) 8%	Background/rationale (item 2) 100%
Loss to follow-up addressed (item12d) 8%	Key results in discussion (item 18) 100%
Non-participation reasons (item 13b) 12%	Objectives (item3) 96%
Missing data addressed (item 12c) 16%	Limitations of the study (item 19) 92%
Sensitivity analysis (item 12e) 20%	Study's design in title/abstract (item 1a) 88%
Quantitive variables (item 6b) 20%	Setting in methods (item 5) 88%
Bias (item 9) 24%	Eligibility/matching criteria for participants (item 6a) 84%
	Outcome data (item 15) 84%
	Interpretation (item 20) 84%

Table 4 **Comparison between the journals which endorse STROBE and those they don't**.

Recommendation	Combined All Journals % (n=25)	Journals endorsing STROBE % (n=6)	Journals not endorsing STROBE % (n=19)	P-value (two-tailed)
Title & Abstract				
1a. Study's design in the title or the abstract	88,0 (22)	100,0 (6)	84,2 (17)	0,358
1b. Informative and balanced summary in the abstract	100,0 (25)	100,0 (6)	100,0 (19)	-
Introduction				
2. Scientific background and rationale	100,0 (25)	100,0 (6)	100,0 (19)	-
3. Objectives	96,0 (24)	100,0 (6)	94,7 (18)	0,524
Methods				
4. Key elements of study design early in the paper	52,0 (13)	83,3 (5)	42,1 (8)	0,225
5. Setting (locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection)	88,0 (22)	83,3 (5)	89,4 (17)	0,826
6a. Eligibility criteria, and the sources and methods of selection of participants / methods of follow-up	84,0 (21)	83,3 (5)	84,2 (16)	0,884
6b. Matching criteria and number of exposed and unexposed	56,0 (7)	33,3 (2)	26,3 (5)	0,968
7. Variables (outcomes, exposures, predictors, potential confounders, effect modifiers)	56,0 (14)	33,3 (2)	63,1 (12)	0,085
8. Data sources/ measurement	56,0 (14)	66,6 (4)	52,6 (10)	0,332
9. Bias	24,0 (6)	16,6 (1)	26,3 (5)	0,739
10. Study Size	48,0 (12)	50,0 (3)	52,6 (10)	0,748
11. Quantitative Variables	20,0 (5)	16,6 (1)	21,0 (4)	0,656
12a. All statistical methods	84,0 (21)	66,6 (4)	89,4 (17)	0,022
12b. Methods used to examine subgroups and interactions	48,0 (12)	33,3 (2)	42,1 (8)	0,467
12c. Missing data	16,0 (4)	0,0 (0)	21,0 (4)	0,174
12d. loss to follow-up OR matching of cases and controls OR sampling strategy	8,0 (2)	0,0 (0)	10,5 (2)	0,358
12e. sensitivity analyses	20,0 (5)	33,3 (2)	21,0 (4)	0,739
Results				
13a. Numbers of individuals at each stage of study	68,0 (17)	83,3 (5)	63,1 (12)	0,236
13b. reasons for non-participation at each stage	12,0 (3)	0,0 (0)	15,7 (3)	0,250
13c. use of a flow diagram	32,0 (8)	50,0 (3)	26,3 (5)	0,468
14a. Characteristics of study participants (eg demographic, clinical, social)	84,0 (21)	100,0 (6)	78,9 (15)	0,174
14b. Number of participants with missing data	4,0 (1)	0,0 (0)	5,2 (1)	0,524

14c. Summarise follow-up time	24,0 (6)	50,0 (3)	15,7 (3)	0,169
15. Outcome Data	84,0 (21)	100,0 (6)	84,2 (16)	0,250
16a. unadjusted estimates, confounder-adjusted estimates and their precision	76,0 (19)	66,6 (4)	78,9 (15)	0,739
16b. Category boundaries	8,0 (2)	0,0 (0)	10,5 (2)	0,358
16c. Translating estimates of relative risk into absolute risk for a meaningful time period	N/A	N/A	N/A	-
17. Other analyses	52,0 (13)	66,6 (4)	42,1 (8)	0,144
Discussion				
18. Key Results	100,0 (25)	100,0 (6)	100,0 (19)	-
19. Limitations	92,0 (23)	100,0 (6)	89,4 (17)	0,358
20. Interpretation	84,0 (21)	100,0 (6)	78,9 (15)	0,174
21. Generalisability	56,0 (14)	50,0 (3)	57,8 (11)	0,943
Other Information				
22. Funding	60,0 (15)	100,0 (6)	47,3 (9)	0,011

Annex: Results of the research

				TITLE/ABSTRACT		INTRODUCTION	
ID	YEAR	SUPPORTIVE	JOURNAL	1a.Study's design indication	1b.Informative and balanced summary in the abstract	2.Background/Rationale	3.Objectives
1	2016	1	Lancet Oncol	1	1	1	1
2	2015	1	BMJ	1	1	1	1
3	2016	0	Br. J Cancer	1	1	1	1
4	2015	0	Am J Public Health	1	1	1	1
5	2014	0	Vaccine	0	1	1	1
6	2014	0	Ann Rheum Dis.	1	1	1	1
7	2015	0	Bull Cancer	1	1	1	1
8	2014	0	BMC Infect Dis.	1	1	1	1
9	2015	0	J Med Internet Res.	1	1	1	1
10	2015	0	Sex Transm Dis.	1	1	1	1
11	2014	0	J Adolesc Health	1	1	1	1
12	2014	0	Gynecol Oncol.	0	1	1	0
13	2013	0	J Natl Cancer Inst.	1	1	1	1
14	2011	1	PLoS One	1	1	1	1
15	2011	0	Vaccine	1	1	1	1
16	2016	0	BMC Womens Health	1	1	1	1
17	2015	0	Vaccine	1	1	1	1
18	2015	0	CMAJ	1	1	1	1
19	2015	1	PLoS One	1	1	1	1
20	2014	1	PLoS One	1	1	1	1
21	2014	0	BMC Public Health.	1	1	1	1
22	2013	1	PLoS One	1	1	1	1
23	2013	0	BMC Public Health	1	1	1	1
24	2014	0	Asian Pac J Cancer Prev.	1	1	1	1
25	2010	0	BMC Womens Health	1	1	1	1

METHODS													
.Study Design	5.Setting	6.Participants		7.Variables	8.Data Sources/ measurement	9.Bias	10.Study Size	11.Quantitative variables	12.Statistical Methods				
		6a	6b						12a	12b	12c	12d	12e
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0	0	1	0	0	0	0	0	0	1	1	0	0	1
1	1	1	0	1	1	0	1	1	1	1	1	1	0
1	1	1	1	1	0	0	0	0	1	0	1	0	0
1	1	0	1	1	1	0	0	1	1	1	0	0	0
0	1	1	0	0	0	0	0	0	1	0	0	0	0
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0	1	1	1	1	1	1	0	1	1	0	0	0	1
1	1	1	N/A	0	0	0	1	0	0	0	0	1	0
1	1	1	0	0	0	0	1	0	1	1	1	0	0
1	0	0	N/A	0	1	0	0	0	0	0	0	0	0
0	1	1	N/A	1	1	1	1	0	1	1	0	0	0
0	1	1	N/A	1	0	1	1	0	1	0	0	0	0
0	1	0	0	0	1	0	1	0	1	1	0	0	0
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0	1	1	N/A	0	0	0	0	0	0	0	0	0	0
1	1	1	N/A	0	0	0	0	0	1	0	0	0	0
0	1	0	N/A	1	0	0	0	0	1	0	1	0	0
1	1	1	N/A	1	0	0	1	0	1	0	0	0	1

RESULTS										
13.Participants			14.Descriptive Data			15.Outcome Data	16.Main Results			17.Other analysis
13a	13b	13c	14a	14b	14c		16a	16b	16c	
1	0	1	1	0	1	1	1	0	N/A	0
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1	0	0	1	0	0	0	1	0	N/A	1
0	0	0	1	0	1	1	1	1	N/A	1
1	1	1	1	0	0	1	1	0	N/A	0
1	1	1	0	0	1	1	1	0	N/A	1
1	0	0	0	0	0	0	1	0	N/A	0
0	0	0	0	0	N/A	1	1	0	N/A	1
1	0	0	1	0	0	1	1	0	N/A	1
1	0	0	1	0	0	1	1	0	N/A	0
0	0	0	1	0	0	1	1	0	N/A	0
0	0	0	1	0	N/A	0	0	0	N/A	0
1	0	0	0	0	0	1	1	0	N/A	1
0	0	0	1	0	N/A	1	0	0	N/A	1
1	0	0	1	0	N/A	1	1	0	N/A	1
1	1	1	1	1	N/A	1	1	1	N/A	1
0	0	0	1	0	0	1	1	0	N/A	0
0	0	1	1	0	0	1	1	0	N/A	0
1	0	0	1	0	1	1	1	0	N/A	1
1	0	1	1	0	0	1	1	0	N/A	1
1	0	0	1	0	1	1	0	0	N/A	0
1	0	0	1	0	N/A	1	0	0	N/A	0
1	0	1	1	0	N/A	1	0	0	N/A	0
1	0	0	1	0	N/A	1	0	0	N/A	0
0	0	0	1	0	N/A	1	1	0	N/A	0

DISCUSSION				OTHER INFORMATION
18.Key Results	19.Limitations	20.Interpretation	21.Generalizability	22.Funding
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1	1	0	1	1
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1	1	1	0	0
1	1	0	0	1
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1	1	1	1	0
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1	1	1	1	1
1	1	1	1	1
1	1	1	0	0
1	1	1	1	0
1	1	1	1	0